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Zwitterionic Borane Adducts of N-Heterocyclic Carbenes from Mesomeric Betaines of Uracil.

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We prepared a series of imidazolium-substituted uracil-anions which are members of the class of cross-conjugated heterocyclic mesomeric betaines. They are in tautomeric equilibrium with their N-heterocyclic carbenes, uracil-6-yl-imidazol-3-ylidenes. These carbenes can be trapped by reaction with sulfur, selenium, as well as by triethylborane and triphenylborane, respectively. The latter mentioned trapping reaction yielded first representatives of a new heterocyclic zwitterionic ring system, imidazo[2',1':3,4][1,4,2]diazaborolo[1,5-c]pyrimidinium-10-ide. Results of two single crystal X-ray structure analyses are presented.

Introduction

Uracil 1 is one of the four nucleobases of RNA and its derivatives display a broad variety of biological activities.1 Due to lactim-lactam tautomerism uracil can exist in six tautomeric forms, two of which are shown in Scheme 1. Spectroscopic examinations as well as calculations reveal that the diketo tautomer is the predominant form in the solid state and in solution.2 The two oxygen atoms of uracil were calculated to be the most susceptible sites of attachments of complex formations3 and numerous complexes through the O4 site,4 or through the N3 / O4 and O4 / N3 / O25 sites have been described. Some uracil metal complexes through the deprotonated N1 site are known as well.6 To our surprise, only very few information is available concerning the interaction of uracils with boranes.8

Scheme 1.

In view of the current interest in the area of overlap between the chemistry of N-heterocyclic carbenes (NHC) and the chemistry of heterocyclic mesomeric betaines (MB)7 we aimed at mesomeric betaines of uracil-6-yl-imidazolium betaines 2 which give rise to betaine 2 – N-heterocyclic carbene 3 tautomerism. Borane adduct formation from N-heterocyclic carbenes is a considerably growing field of chemistry9 so that we intended to explore the behavior of our target compounds toward boranes.

Scheme 2.

Mesomeric betaines such as 2 are defined as neutral compounds which can exclusively be represented by dipolar resonance forms in which the positive and negative charges are delocalized within a common π-electron system. Four distinct main classes are distinguished, i) conjugated mesomeric betaines (CMB), ii) ylides, iii) cross-conjugated (CCMB) mesomeric betaines, and iv) pseudo-cross-conjugated mesomeric betaines (PCCMB).11,12 The relationships to normal (NHC), abnormal (aNHC)13 [sometimes called mesoionic carbenes (MIC)14] and remote N-heterocyclic carbenes (rNHC)15 are summarized in reviews on betaine – carbone interconversions,9 betaine and carbone chemistry of pyrazoles and indazoles,16 or complex chemistry.17

Betaine – carbene interconversions can be achieved by decarboxylations, deprotonations, and tautomerisms starting from suitable betaines. Members of the class of PCCMBs11,12 such as imidazolium-2-carboxylates 318 and pyrazolium-3-carboxylates19 are convenient precursors of normal N-heterocyclic carbenes such as 4 (Scheme 3). On the other hand, PCCMBs can be formed by trapping reactions of NHCs with heterocumulenes.9,20 Decarboxylations of CCMBs such as imidazolium-4-carboxylate 5 and pyrazolium-4-carboxylate 7 to give the aNHC 6 or the rNHC 8 require harsh conditions, and, as a consequence, only few examples of successful conversions exist.21 The latter molecule 8 has been described as dipolar structure as shown and as cyclic bent allene, and has been studied intensively.22
Deprotonations of mesomeric betaines results in the formation of anionic N-heterocyclic carbenes. Examples are the anions of the CMB imidazolium-4-olate, the CCMB pyrimidinium-olate and the CMB sydnone (Scheme 4).

Tautomerism of a mesomeric betaine to an N-heterocyclic carbene has surprisingly been observed on examination of the mesoionic compound (Busch’s reagent, nitron) which is in equilibrium with (Scheme 5). Correspondingly imidazolium-4-aminide is in tautomeric equilibrium with carbene.

We investigated tautomeric equilibria of the ylides imidazolium-indolates with their corresponding N-heterocyclic carbenes. The carbenes can be trapped with boranes to give first representatives of a new heterocyclic ring system, a zwitterionic imidazo[2',1':3,4][1,4,2]diazaborolo[1,5-c]pyrimidinium-10-ide.

Results and Discussion

In continuation of our earlier work on uracils, we reacted 6-chlorouracil (6-chloropyrimidine-2,4(1H,3H)-dione) with the imidazoles and obtained the imidazolium salts in moderate to excellent yields (Scheme 7).

The resonance frequency of of the uracil ring is diagnostic for the success of the deprotonation, as it shifts upfield by 0.15 – 0.54 ppm in the $^1$H NMR spectra, depending on the substitution pattern. The betaines are soluble in water and other highly polar solvents such as DMSO and methanol, but almost insoluble in acetonitrile or chloroform. In the spectra of NMR...
measurements taken in DMSO-d$_6$ only the betaine tautomer of 2a-e can be seen. No traces of the N-heterocyclic carbene 3a-e are visible under these conditions. At least in part this can be explained by the solubility of 2a-e which compelled us to use highly polar solvents for the characterization. The betaines 2a-e belong to the class of cross-conjugated heterocyclic mesomeric betaines (CCMB). Characteristically, the charges are restricted to separate parts of the common π-electron system in the resonance forms (I). The anionic part of the molecule is joined to the cationic part through a union bond which starts from an unstarred position of the isoconjugated equivalent of the π-electron system which delocalizes the negative charge (II). This is a nodal (inactive) position of the highest occupied molecular orbital (HOMO) (III) which induces the charge separation in the ground state in cross-conjugated mesomeric betaines.$^{1,12,30}$

Figure 1.

In the presence of trapping reagents, the equilibrium can be shifted toward the N-heterocyclic carbene tautomer 3a. Thus, in the presence of sulfur and selenium, respectively, the thione 23 and the selenone 24 were formed in high yields (Scheme 8).

![Scheme 8](image)

Similarly, triethylborane in dioxane converted the betaine-NHC equilibrium into the new ring system of imidazo[2’,1’][1,4,2]diazaborole[1,5-c]pyrimidinium-10-ides 25a-e as fluorescent crystalline solids (Scheme 9). A similar series of reactions was performed with triphenylborane so that 2a-d were converted into 26a-d which were also obtained as crystalline compounds. Betaine 2e, however, did not react under these conditions. The resonance frequency of 5-H of the uracil moiety was detected between 5.96 ppm and 6.01 ppm (25) and between 6.20 ppm and 6.32 ppm (26), and the $^1$B NMR signals appear between -1.6 ppm and 1.4 ppm depending on the solvent and the substitution pattern of the borane adduct, respectively. Thermogravimetric analyses show that decomposition of 25a, 25c, and 25d occurs above 270 °C in the solid state. The borane adducts proved to be stable towards acids. Thus, after treatment of 25a with trifluoroacetic acid in methanol at reflux temperature we were able to recover the material unchanged.

![Scheme 9](image)

Single crystals of the boron adducts 25b and 25d were obtained by slow evaporation of concentrated solutions in ethanol. Results of single crystal X-ray analyses are as follows. The zwitterions 25b (Figure 2) and 25d (Figures 3 and 4) crystallized monoclinic and orthorhombic, respectively. In 25b the ethyl-hydroxy group is disordered. The B-C$_\text{arbene}$ bond length [B-C11; crystallographic numbering] were determined to be 161.8(4) pm (25b) and 160.7(5) pm (25d), and the B-N$_\text{arbene}$ bonds 162.3(3) pm and 162.8(4) pm, respectively. The corresponding bond angles N1-B1-C11 were determined to be 92.37(19)$^\circ$ (25b) and 92.2(3)$^\circ$ (25d). The three rings, uracil, diazaborole, and imidazole are almost planar and dihedral angles N1-C2-N3-C4 = 1.8(5)$^\circ$ / -0.3(4)$^\circ$, C11-B1-N1-C6 = -1.0(3)$^\circ$ / -1.2(3)$^\circ$, and N7-C8-C9-N10 = -0.3(4)$^\circ$ / -0.2(3)$^\circ$ were measured in 25b and 25d, respectively. In 25b hydrogen bonds were found between O2 and the ethyl-hydroxy group with N3-H and O4 of a neighbouring molecule, respectively.

![Figure 2](image)
We present first examples of cross-conjugated heterocyclic mesomeric betaines which are in tautomeric equilibrium with their N-heterocyclic carbenes. Thus imidazolium-uracilates undergo tautomerism to uracil-6-yl-imidazol-3-ylides. All spectroscopic data are in agreement to those reported earlier. Recrystallization from water yielded 197 mg (98%) of a white solid. All melting points are uncorrected and were determined in an apparatus according to Dr. Tottoli (Büchi). Yields are not optimized. The compounds 22a and 2a were reported in one of our earlier publications.

3-(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1-methyl-1H-imidazolium chloride 22a. A solution of 147 mg (1.0 mmol) of 20 and 288 mg (2.0 mmol) of 21a in 15 mL of chlorobenzene was heated under reflux for 8 h. After cooling, a fine, light yellow precipitate, which was filtered off and thoroughly washed with diethyl ether. Recrystallization from water yielded 224 mg (98%) of a white solid. All spectroscopic data are in agreement to those reported earlier.

3-(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1-phenyl-1H-imidazolium chloride 22b. A solution of 147 mg (1.0 mmol) of 20 and 224 mg (2.0 mmol) of 21b in 15 mL of chlorobenzene was heated under reflux for 8 h. After cooling, a fine, gray precipitate, which was filtered off and thoroughly washed with diethyl ether. Recrystallization from water yielded 242 mg (83%) of light yellow solid.

3-(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1-(2-hydroxyethyl)-1H-imidazolium chloride 22c. A solution of 147 mg (1.0 mmol) of 20 and 228 mg (2.0 mmol) of 21c in 15 mL of chlorobenzene was heated under reflux for 8 h. After cooling, a fine, light yellow precipitate formed, which was filtered off and thoroughly washed with diethyl ether. Recrystallization from water yielded 242 mg (83%) of light yellow solid.

3-(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1-vinyl-1H-imidazolium chloride 22d. A solution of 147 mg (1.0 mmol) of 20 and 286 mg (2.0 mmol) of 21d in 15 mL of chlorobenzene was heated under reflux for 8 h. After cooling, a fine, light yellow precipitate formed, which was filtered off and thoroughly washed with diethyl ether. Recrystallization from water yielded 255 mg (98%) of a white solid. All spectroscopic data are in agreement to those reported earlier.

1-Benzyl-3-(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1-methyl-1H-imidazolium chloride 22e. A solution of 147 mg (1.0 mmol) of 20 and 316 mg (2.0 mmol) of 21e in 15 mL of chlorobenzene was heated under reflux for 8 h. After cooling, a fine, light yellow precipitate formed, which was filtered off and thoroughly washed with diethyl ether. Recrystallization from water yielded 316 mg (98%) of a white solid. All spectroscopic data are in agreement to those reported earlier.

Conclusions

We present first examples of cross-conjugated heterocyclic mesomeric betaines which are in tautomeric equilibrium with their N-heterocyclic carbenes. Thus imidazolium-uracilates undergo tautomerism to uracil-6-yl-imidazol-3-ylides. Trapping reactions were performed with sulfur and selenium to give an imidazole-thione and -selenone, respectively. Triethylborane and triphenylborane give first representatives of a new heterocyclic zwitterionic ring system, imidazo[2,1-d:1,2-d]imidazol[1,5-c]pyrimidin-10-ide. These results supplement our knowledge about the interesting area of overlap between mesomeric betaines and N-heterocyclic carbenes.

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Experimental

General considerations. Flash-chromatography was performed with silica gel 60 (0.40-0.63 mm). Nuclear magnetic resonance (NMR) spectra were obtained with Bruker Avance 400 and Bruker Avance III 600 MHz instruments. 1H NMR spectra were recorded at 400 MHz or 600 MHz. 13C NMR spectra were recorded at 100 MHz or 150 MHz. 19F NMR spectra were recorded at 282 MHz. 31P NMR spectra were recorded at 202 MHz. 31P NMR spectra were recorded at 121 MHz. 11B NMR spectra were recorded at 128 MHz or 192 MHz. Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. FT-IR spectra were obtained on a Bruker Vector 22 in the range of 400 to 4000 cm-1. ATR-IR spectra were obtained on a Bruker Alpha in the range of 400 to 4000 cm-1. The mass spectra were measured with a Varian 320-M Triple Quadrupole Mass Spectrometer with a Varian 450-GC. The electrospray ionization mass spectra (ESIMS) were measured with an Agilent LCMSD series HP 1100 with APIES. Melting points are uncorrected and were determined in an apparatus according to Dr. Tottoli (Büchi). Yields are not optimized. The compounds 22a and 2a were reported in one of our earlier publications.

3-(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1-methyl-1H-imidazolium chloride 22a. A solution of 147 mg (1.0 mmol) of 20 and 164 mg (2.0 mmol) of 21a in 15 mL of chlorobenzene was heated under reflux for 8 h. After cooling, a fine, nearly white precipitate deposited, which was filtered off and thoroughly washed with diethyl ether. Recrystallization from water yielded 224 mg (98%) of a white solid. All spectroscopic data are in agreement to those reported earlier.

3-(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1-phenyl-1H-imidazolium chloride 22b. A solution of 147 mg (1.0 mmol) of 20 and 224 mg (2.0 mmol) of 21b in 15 mL of chlorobenzene was heated under reflux for 8 h. After cooling, a fine, gray precipitate, which was filtered off and thoroughly washed with diethyl ether. Recrystallization from water yielded 242 mg (83%) of light yellow solid.

3-(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)-1-vinyl-1H-imidazolium chloride 22d. A solution of 147 mg (1.0 mmol) of 20 and 286 mg (2.0 mmol) of 21d in 15 mL of chlorobenzene was heated under reflux for 8 h. After cooling, a fine, light yellow precipitate formed, which was filtered off and thoroughly washed with diethyl ether. Recrystallization from water yielded 255 mg (98%) of a white solid. All spectroscopic data are in agreement to those reported earlier.
8.02 (m, 1H), 7.25 (dd, J = 15.5 / 8.6 Hz, 1H), 6.11 (s, 1H), 5.98 (dd, J = 15.5 / 3.1 Hz, 1H), 5.60 (dd, J = 8.6 / 3.1 Hz, 1H) ppm; 13C NMR (100 MHz, DMSO-d6): δ = 169.4, 160.5, 155.8, 128.1, 120.2, 119.8, 111.1, 87.0 ppm; IR (ATR): 3372, 3110, 2966, 1676, 1623, 1490, 1085, 795, 781, 612, 448 cm⁻¹; HR-ESI-MS for C20H15N5O3 required 326.1073. Found 326.1072.

6-(Methyl-2-thioxo-2,3-dihydro-1H-imidazol-1-yl)pyrimidine-2,4(1H,3H)-dione 2c. 326 mg (1 mmol) of caesium carbonate was added to a suspension of 96 mg (0.5 mmol) of 22a and 47 mg (0.6 mmol) of sulfur in 15 mL of dry acetonitrile. The mixture was heated under a nitrogen atmosphere under reflux for 7 h. After cooling, the solvent was evaporated in vacuo. The product was separated with column chromatography (pure ethyl acetate). Evaporation to dryness in vacuo formed a yellow solid: yield 82 mg (73%); dec > 320 °C; 1H NMR (400 MHz, DMSO-d6): δ = 9.77 (s, 1H), 7.62 (d, J = 2.6 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 6.78 (s, 1H), 3.48 (s, 3H) ppm; 13C NMR (100 MHz, DMSO-d6): δ = 167.0, 160.9, 158.7, 157.0, 118.4, 115.5, 88.0, 34.4 ppm; IR (ATR): 3114, 2915, 2812, 1683, 1617, 1564, 1399, 1366, 1268, 1283, 1181, 531, 431 cm⁻¹; HR-ESI-MS for C17H13N5O3 required 223.0290. Found 223.0285.
A solution of 460 mg (5 mmol) of $\text{BET}_2$ in 2 mL of dichloromethane was added to a suspension of 111 mg (0.5 mmol) of $\text{BPh}_3$ in 2 mL of dichloromethane. The mixture was stirred at 200 °C under a nitrogen atmosphere in a Schlenk-tube for 24 h. After cooling, the solvent was evaporated in vacuo. The product was separated by column chromatography (ethyl acetate : ethanol = 2 : 1). After evaporating to dryness in vacuo, recrystallization from ethanol formed a white solid: yield 91 mg (51%); dec > 352 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ = 10.73 (s, 1H), 8.33 (s, 1H), 8.25 (s, 2H), 8.07 (d, $J = 8.1$ Hz, 1H), 7.47-7.41 (m, 2H), 7.38 (s, 1H), 7.30-7.25 (m, 1H), 7.20-7.15 (m, 3H), 7.06-7.02 (m, 1H), 7.02-6.98 (m, 1H), 6.96 (s, 1H), 6.88 (s, 1H), 4.60 (2H), 4.38 (2H), 3.53 (2H), 3.50 (2H), 2.76-2.72 (m, 2H), 2.53-2.49 (m, 2H), 2.36-2.32 (m, 2H), 2.17-2.13 (m, 2H), 2.03-2.00 (m, 2H), 1.96-1.92 (m, 2H), 1.87-1.83 (m, 2H), 1.80-1.76 (m, 2H), 1.71-1.67 (m, 2H), 1.60-1.54 (m, 2H), 1.47-1.43 (m, 2H), 1.39-1.35 (m, 2H), 1.27-1.23 (m, 2H), 1.15-1.11 (m, 2H), 1.00-0.95 (m, 2H), 0.77 (t, $J = 6.9$ Hz, 3H), 0.70 (t, $J = 6.9$ Hz, 3H), 0.34 (t, $J = 6.9$ Hz, 3H). 

Notes and references


